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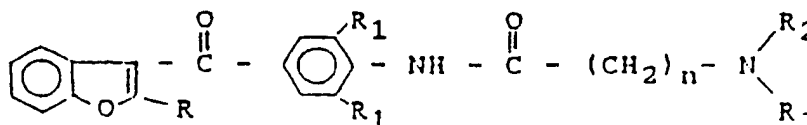
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(54) 2-Alkyl-3-benzoylbenzofurans and pharmaceutical compositions containing them.

(57) Novel alkyl-benzoylbenzofurans are disclosed. The novel compound have the formula



wherein R is an alkyl group containing 2 to 4 carbon atoms, R₁ is an alkyl group containing 1 to 4 carbon atoms, R₂ and R₃ are each an alkyl group containing 1 to 3 carbon atoms and n is an integer of 1 or 2. The compounds of the invention are useful for the treatment of cardiac arrhythmia and pharmaceutical compositions containing above compounds as active material are also disclosed.

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2-ALKYL-3-BENZOYLBENZOFURANS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Field of the Invention

The invention pertains to new alkylbenzoylbenzofurans and more particularly to new 2-alkyl-3-[4-(omega-N,N-dialkylaminoacylamino) - 3,5-dialkylbenzoyl] benzofurans as well as to pharmaceutical compositions for the treatment of cardiac arrhythmia containing these benzofurans.

Background of the Invention

Cardiac arrhythmia is an important cause of death following myocardial infarction or from other cardiac pathology. Heretofore, drugs used to control this disorder such as quinidine, lidocaine and procainamide have manifested significant drawbacks. According to Goodman and Gilman, in the Pharmacologic Basis of Therapeutics, 7th edition, pp.761 - 770, "About one third of the patients who receive quinidine will have immediate adverse effects that necessitate discontinuation of therapy....Procainamide is useful for the treatment of a variety of arrhythmias, and it can be administered by several routes. Unfortunately its potency and versatility are marred by its short duration of action and high incidence of adverse reactions when it is used chronically.... Lidocaine has a narrow antiarrhythmic spectrum....The main adverse effects are on the central nervous system....Higher concentrations may cause decreased hearing, disorientation, muscle twitching, convulsions or respiratory arrest."

The great need for improved antiarrhythmics is evident.

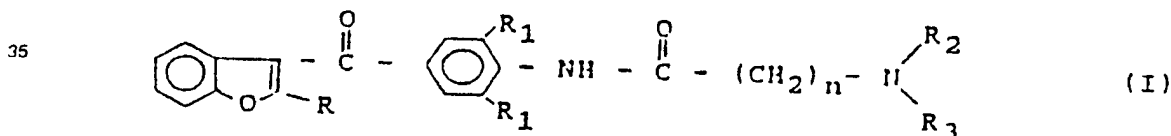
Summary of the Invention

An object of this invention is the provision of new compounds which have improved antiarrhythmic activity.

A particular object of this invention is the provision of new 2-alkyl-3-benzoylbenzofurans which have improved antiarrhythmic activity.

A further object of this invention is the provision of new pharmaceutical compositions useful for treating arrhythmia.

These objects and others which will become evident from the description below are accomplished by the new 2-alkyl-3-benzoylbenzofurans of the following formula (I)



wherein

R is an alkyl group containing 2 to 4 carbon atoms,

R₁ is an alkyl group containing 1 to 4 carbon atom

R₂ and R₃ are each an alkyl group containing 1 to 3 carbon atoms and

n is an integer of 1 or 2 and

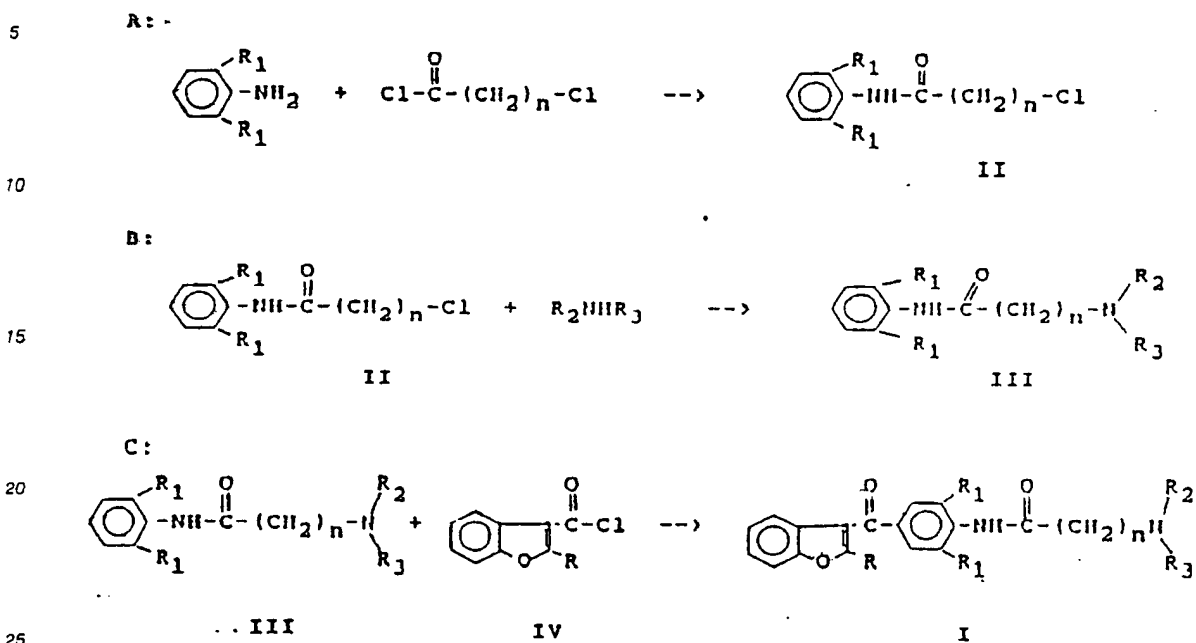
pharmaceutically acceptable salts thereof.

We have found that compounds of formula (I) display highly antiarrhythmic activity and thus provide an improved method for the treatment of arrhythmia.

Detailed Description of the Invention

Compounds of formula (I) wherein R is C₂H₅, n-C₃H₇, and n-C₄H₉ are preferred, as are compounds of formula (I) wherein R₁ is CH₃, C₂H₅, i-C₃H₇ and t-C₄H₉. Another group of preferred compounds are those wherein R₂ and R₃ are both C₂H₅.

The preparation of compounds of formula (I) of the invention can be accomplished according to the following series of reactions.



wherein R, R₁, R₂, R₃ and n are as defined above.

To prepare 2,6-dialkyl-α-chloroacetylanilide (II) where n=1 or 2,6-dialkyl-β-chloropropionylanilide (II) where n=2 is shown in step A, chloroacetyl chloride or β-chloropropionyl chloride is reacted with a 2,6-dialkylaniline in an inert solvent such as a lower fatty acid or a lower fatty acid ester, as described for example in U.S. Patent No. 2,441,498.

The dialkyl-chloroacylanilide (II) is then reacted with a sec-amine in a refluxing hydrocarbon solvent as shown in step B.

This reaction has also been described in the above-noted U.S. Patent. After separation and purification, the 2,6-dialkyl-ω-N,N-dialkylaminoacylanilide product (III) is obtained.

As shown in step C, compound (I) of the invention is obtained by reacting 2-alkylbenzofuran-3-carboxylic acid chloride (IV) with 2,6-dialkyl-ω-N,N-dialkylaminoacylanilide (III). This reaction is carried out in an inert solvent by means of a Friedel-Crafts system with a Lewis acid catalyst.

Compounds of the invention have improved antiarrhythmic activity. For example, 2-ethyl-3-[4-(N,N-diethylaminoacetyl)amino]-3,5-dimethylbenzoyl]benzofuran, (the compound of formula (I) wherein R = C₂H₅, R₁ = CH₃, R₂ and R₃ = C₂H₅ and n = 1), when compared with lidocaine in a rat coronary ligation model, displayed superior activity in suppressing both ventricular fibrillation and ventricular tachycardia, and was comparable in promoting survival of challenged animals. Thus, compounds of formula (I) can provide an improved level of antiarrhythmic activity together with diminished side effects.

The antiarrhythmic compounds of formula (I) can be formulated for use by the oral or parenteral routes. Acute emergency treatment would normally employ an intravenous form containing ~~as an active agent~~, a pharmaceutically acceptable salt of the antiarrhythmic compound of formula (I) such as an hydrochloride, sulfate or a phosphate salt in an aqueous vehicle compatible with body fluids. The sterile, isotonic solution for such use is comprised of the soluble salt of the active drug in citrate, phosphate or other physiological acceptable buffer in the pH range of 4.0 - 7.0. Preservatives such as benzyl alcohol, methyl "Parabens" or propyl "Parabens", esters of p-hydroxybenzoic acid sold by Napp Chemicals, may be used, particularly in multiple dose formulations, to maintain sterility. Typical intravenous or intramuscular preparations may contain from 10mg to 100mg of the active compound, calculated as base, per ml of solution. Administration of 0.5 - 10 mg of active compound per kg of patient body weight by the I.V. or I.M. route every 6 - 8 hours may be continued until a satisfactory cardiac rhythm is established.

Chronic therapy is customarily maintained by means of oral tablets or capsules containing 10 - 200 mg of a compound of formula (I) per dose. As is usual in this art, the active compound is admixed with excipients such as lactose, starch, "Avicel" or the like, together with lubricants and dispersants such as

stearic acid, magnesium stearate, silica, etc. in amounts necessary to confer appropriate disintegration and dissolution properties to the dosage form.

The usual antiarrhythmic maintenance dose will be in the range of 1 - 100 mg of active compound per kg of patient body weight daily, delivered in 3 to 4 divided doses or in a single sustained-release dose.

The following examples further illustrate the invention but must not be construed to limit the invention in any manner.

EXAMPLE 1

Step A. Preparation of N-Acylaminoanilide (II) by Reaction of 2,6-Dialkylaniline with omega-Chloroacyl Chloride

One mole of 2,6-dimethylaniline is dissolved in 800 ml of glacial acetic acid. The mixture is cooled to 10° C., after which 1.1 mole of alpha-chloroacetyl chloride is added rapidly. The mixture is agitated vigorously for two minutes, whereupon 1000 ml of aqueous sodium acetate (250 g. of sodium acetate per liter of water) is added rapidly with continuous agitation. Agitation is continued for one-half hour; the precipitate which has formed is separated by filtration, washed with water and dried carefully in vacuo at 50° C. The yield of 2,6-dimethyl-alpha-chloroacetanilide is 70 - 80% of the theoretical.

Following the same procedure, 2,6-diethylaniline, 2,6-diisopropylaniline or 2,6-di-tert-butylniline is caused to react with alpha-chloroacetyl chloride to yield the corresponding alpha-chloro-2,6-dialkylacetanilide of formula (II).

Likewise any aniline identified above is caused to react with beta-chloropropionyl chloride to provide the corresponding beta-chloro-2,6-dialkyl-propionanilide of formula (II).

EXAMPLE 2

Step B. Preparation of N,N-Dialkylaminoacyl-2,6-dialkylanilide (III) by Reaction of omega-Chloroacyl-2,6-dialkylanilide (II) with a sec-Amine

One mole of alpha-chloroacetyl-2,6-dimethylanilide and 3 moles of diethylamine are dissolved in 1000 ml of dry benzene.

The mixture is heated at reflux for 4 hours. The precipitated diethylamine hydrochloride is separated by filtration and the benzene solution is washed with 3 N hydrochloric acid twice (600 ml each time). The aqueous acid extracts are made strongly basic by the addition of 30% aqueous sodium hydroxide. The resulting oily precipitate which separates is taken up in diethyl ether (1 liter), the ether phase is dried over anhydrous potassium carbonate, and the resulting dry, filtered ether solution is distilled. Following distillation of the ether at atmospheric pressure, the remainder of the fractionation is carried out in vacuo at about 2 mm Hg pressure. The product, alpha-diethylamino-2,6-dimethylacetanilide boils at about 159-160° C at 2 mm Hg. It crystallizes in the receiver and the crystalline product melts at 68-69° C. The yield is 95% of theoretical.

Using the same procedure, each of the three other alpha-chloro-2,6-dialkylacetanilides prepared as in Example 1 is caused to react with diethylamine to yield the corresponding alpha-diethyl-amino-2,6-dialkylacetanilide of formula (III).

Using the same procedure, each of the four beta-chloropropionyl-2,6-dialkylanilides prepared according to Example 1 is caused to react with diethylamine to provide the corresponding beta-diethylaminopropionyl-2,6-dialkylanilide of formula (III).

When dimethylamine or dipropylamine is employed in this example, in place of diethylamine, the corresponding dimethylamino or dipropylamino product of formula (III), wherein both R₂ and R₃ are either CH₃ or C₃H₇, respectively, results.

EXAMPLE 3

Step C. Preparation of 2-Alkyl-3-[4-(omega-N,N-dialkylaminoacyl-amino)-3,5-dialkylbenzoyl]benzofuran (I) by Friedel-Crafts Acylation of the Anilide (III) with 2-Alkyl-3-benzofuroyl Chloride (IV)

2-Ethylbenzofuran-3-carboxylic acid chloride (0.45 g.; 2.1 m. moles) and alpha-diethylamino-2,6-dimethyl-acetanilide (0.5 g.; 2.1 m.moles) are dissolved in 1,2-dichloroethane (10 ml) and cooled to 0° C. Anhydrous aluminum chloride (0.43 g.; 3.2 m.moles) is added all at once and the reaction mixture is agitated for 16 hours at room temperature. The 1,2-dichloroethane solvent is then distilled off in vacuo and 10 ml of 5 N aqueous hydrochloric acid is added to the residue. The resulting mixture is agitated for 30 minutes, made basic with aqueous sodium hydroxide and then extracted three times with 20 ml portions of ethyl acetate. The ethyl acetate extracts are dried over anhydrous potassium carbonate and concentrated to a residue. The residue is taken up in a small volume of ethyl acetate and column chromatographed over 100 g. of anhydrous magnesium silicate. The column is eluted with hexane and mixtures of hexane and ethyl acetate, progressively enriched with ethyl acetate in the manner of gradient elution. Homogeneous product fractions, determined by TLC, are combined and crystallized from acetone-hexane, affording 53 mg of 2-ethyl-3-[N,N-diethylamino-acetyl-amino]-3,5-dimethylbenzoyl]benzofuran (I), wherein R = C₂H₅, R₁ = CH₃, R₂ and R₃ = C₂H₅ and n = 1, which has a melting point of 82-85° C.

Reacting 2-n-propylbenzofuran-3-carboxylic acid chloride or 2-n-butylbenzofuran-3-carboxylic acid chloride with alpha-diethyl-amino-2,6-dimethyl-acetanilide (IV) in the same Friedel-Crafts procedure provides the corresponding 2-n-propyl- and 2-n-butylbenzofurans (I).

By reacting 2-ethylbenzofuran-3-carboxylic acid chloride with the dialkylanilide (III), wherein: R₁ = C₂H₅, i-C₃H₇ or t-C₄H₉; R₂ = CH₃ or n-C₃H₇ and n = 1, the corresponding compounds of formula (I) are obtained wherein R₁ and R₂ are as follows :

R ₁	R ₂ and R ₃
C ₂ H ₅	CH ₃
C ₂ H ₅	n-C ₃ H ₇
i-C ₃ H ₇	CH ₃
i-C ₃ H ₇	n-C ₃ H ₇
t-C ₄ H ₉	CH ₃
t-C ₄ H ₉	n-C ₃ H ₇

Reaction of the corresponding 2-n-propylbenzofuran-3-carboxylic acid chloride or 2-n-butylbenzofuran-3-carboxylic acid chloride (IV) affords corresponding compounds of formula (I) according to the choice of R₁, R₂ and R₃. Likewise compounds of formula (I) are provided wherein n = 2, by reacting in the same manner a 2-alkylbenzofuran-3-carboxylic acid chloride (IV) with a beta-diethylaminopropionyl-2,6-dialkylanilide of formula (III).

EXAMPLE 4

Pharmaceutical Compositions

Injectable Composition for I.V. or I.M. Use

Compound (I)*	50 mg
Sodium citrate	2 mg
Sodium chloride	14 mg
Sterile water	1 ml

Tablets, 100 mg

Compound (I)*	100.0 mg
"Avicel" ph 102	83.35 mg
Lactose, spray dried	141.65 mg
Magnesium stearate	6.65 mg
"Cab-O-Sil"	0.50 mg

Tablets of the above formulation are prepared by blending all ingredients, except magnesium stearate, for 25 minutes, then adding the magnesium stearate and blending until homogeneous. The mixture is compressed into tablets using B/32 in standard concave molding. "Avicel" is a microcrystalline cellulose sold by FMC Corporation, Food & Pharmaceutical Products Division, while "Cab-O-Sil" is colloidal silica produced by the Cabot Corporation.

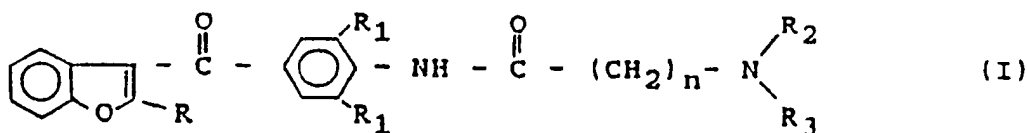
Tablets, 200 mg

Compound (I)*	200.0 mg
"Avicel" ph 102	144.0 mg
Stearic acid powder	9.0 mg
Magnesium stearate	3.2 mg
Compound (I)* in each of the above formulations refers to the HCl form; however, the weights are the weights of the free base.	

Tablets are prepared from the above formulation by blending compound (I) with "Avicel" for 25 minutes, screening in the stearic acid and magnesium stearate and blending for 5 minutes more. The resultant mixture is compressed into tablets using 3/8 inch standard concave tooling.

Claims

1. A 2-alkyl-3-benzoylbenzofuran of the formula



wherein

R is an alkyl group containing 2 to 4 carbon atoms,

R₁ is an alkyl group containing 1 to 4 carbon atoms,

R₂ and R₃ are each an alkyl group containing 1 to 3 carbon atoms and

n is an integer of 1 or 2 and

pharmaceutically acceptable salts thereof.

2. The 2-alkyl -3-benzoylbenzofuran according to Claim 1, in which R is an ethyl, n-propyl or n-butyl group.
3. The 2-alkyl -3-benzoylbenzofuran according to Claim 1, in which R is an ethyl group.
4. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R₁ is a methyl, ethyl, isopropyl or t-butyl group.
5. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R₁ is a methyl group.
6. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R₂ and R₃ are each a methyl, ethyl or propyl group.
7. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R₂ and R₃ are each an ethyl group.
- 10 8. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which n is 1.
9. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which n is 2.
10. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R is an ethyl, n-propyl, or n-butyl group, R₁ is a methyl group, R₂ and R₃ are each a methyl, ethyl or propyl group and n is 1.
11. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R is an ethyl, n-propyl, or n-butyl group, R₁ is a methyl group, R₂ and R₃ are each a methyl, ethyl or propyl group and n is 2.
- 15 12. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, in which R is an ethyl group, R₁ is a methyl group and R₂ and R₃ are each a methyl, ethyl or propyl group.
13. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, which is 2-ethyl-3-[4-(N,N-diethylaminoacetyl-amino-3,5-dimethylbenzoyl)]-benzofuran or a pharmaceutically acceptable salt thereof.
- 20 14. The 2-alkyl-3-benzoylbenzofuran according to Claim 1, which is 2-ethyl-3-[4-(N,N-diethylamino-beta-propionylamino)-3,5-dimethyl-benzoyl]benzofuran or a pharmaceutically acceptable salt thereof.
15. A pharmaceutical composition for treating cardiac arrhythmia comprising a compound according to Claim 1 in a therapeutically effective amount in combination with a pharmaceutically acceptable carrier.
16. A pharmaceutical composition for treating cardiac arrhythmia comprising a compound according to Claim 13 in a therapeutically effective amount in combination with a pharmaceutically acceptable carrier.
- 25 17. A pharmaceutical composition for treating cardiac arrhythmia comprising a compound according to Claim 10 in a therapeutically effective amount in combination with a pharmaceutically acceptable carrier.
18. A pharmaceutical composition for treating cardiac arrhythmia in the form of an oral tablet comprising a compound according to Claim 1 in a therapeutically effective amount in combination with a pharmaceutically acceptable carrier.
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DOCUMENTS CONSIDERED TO BE RELEVANT			EP 89303772.1
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	DE - A1 - 2 710 047 (LABAZ) * Formula I; page 13, lines 6-10 *	1, 15-18	C 07 D 307/81 A 61 K 31/34
A	US - A - 3 331 845 (TOMCUFCIK) * Column 1, lines 15-54 *	1	
A	CHEMICAL ABSTRACTS, vol. 88, no. 5, January 30, 1978, Columbus, Ohio, USA ASTOIN, JACQUES et al. "Study of benzofuran. LIX. Orientation of the arylation of 2-ethylbenzofuran depending on the aroyl chloride used" page 478, column 2, Abstract-no. 37 538z & J.Heterocycl.Chem. 1977, 14(5), 861-6	1	
A	CHEMICAL ABSTRACTS, vol. 88, no. 5, January 30, 1978, Columbus, Ohio, USA ASTOIN JACQUES et al. "Study of benzofuran. LX. Orientation of the alkaline degradation of 3-aryol-2-ethylbenzofurans depending on the aroyl group substituent" page 478, column 2, Abstract-no. 37 539q & J.Heterocycl.Chem. 1977, 14(5), 867-9	1	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 307/00
A	CHEMICAL ABSTRACTS, vol. 87, no. 7, August 15, 1977, Columbus, Ohio, USA GOLDENBERG, CHARLES et al.	1	
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 22-06-1989	Examiner HAMMER
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			



-2-

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
	"Benzofurans. LX. Potential antianginal sulfonylamino-benzoylbenzofurans" page 443, column 2, Abstract-no. 53 009n & Eur.J.Med.Chem.-Chim.Ther. 1977, 12(1), 81-6 -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 22-06-1989	Examiner HAMMER
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